CLAIMS

1. A computer-based method of drug design based on genetic polymorphisms, comprising:

obtaining one or more amino acid sequences of a target protein that is the product of a gene exhibiting genetic polymorphisms, wherein the sequences represent different genetic polymorphisms;

generating 3-dimensional (3-D) protein structural variant models from the sequences; and

based upon the structures of the 3-D models, designing drug candidates or modifying existing drugs based on predicted intermolecular interactions of the drug candidates or modified drugs with the structural variants.

2. The method of claim 1 wherein the structure-based drug design method comprises:

computationally docking the drug candidate or modified drug molecules with the target protein structural variant models;

energetically refining the docked complexes;

determining the binding interactions between the drug candidate or modified drug molecules and the structural variants; and

designing and identifying drugs or modifications to existing drugs based on the binding interactions.

3. The method of claim 2 wherein the binding interactions are determined by:

calculating the free energy of binding between the protein structural variant model and the docked molecule; and

decomposing the total free energy of binding based on the interacting residues in the protein active site.

4. The method of claim 1 wherein:

after the protein structural variant models derived from a particular genetic polymorphism are generated, selected model structures are

analyzed to determine common structural features that are conserved throughout the selected models, wherein

the conserved structural features are used as a basis for structure-based drug design studies.

5. The method of claim 4 wherein the selected model structures represent the structural variants resulting from the most commonly occurring genetic polymorphisms.

6. The method of claim 4 wherein the selected model structures represent the structural variants resulting from genetic polymorphisms found in a specific patient subpopulation.

7. The method of claim 1 wherein the structural variant models are stored in a relational database, comprising:

3-D molecular coordinates for the structural variants;

a molecular graphics interface for 3-D molecular structure visualization; and

functionality for protein sequence and structural analysis; and

database searching tools.

8. The method of claim 7 wherein the database further comprises observed clinical data associated with the genetic polymorphisms.

9. A computer-based method of drug design based on genetic polymorphisms, comprising:

obtaining one or more amino acid sequences of a target protein that is the product of a gene exhibiting genetic polymorphisms, wherein the sequences represent different genetic polymorphisms;

generating 3-D protein structural variant models from the sequences;

computationally docking drug molecules with the target protein models;

energetically refining the docked complexes; and

based on predicted intermolecular interactions of the drugs or drug candidates with the structural variants and using structure-based drug design techniques, identifying potential drug candidates or identifying modifications of existing drugs that are specific for a protein with selected polymorphism or that specifically interact with all proteins exhibiting the polymorphism.

10. The method of claim 9 wherein the structure-based drug design technique comprises:

computationally docking drug or potential new drug candidate molecules with the target protein structural variant models;

energetically refining the docked complexes;

determining the binding interactions between the drug or potential new drug candidate molecules and the structural variants; and

designing potential new drugs or modifications to existing drugs based on the binding interactions.

11. The method of claim 10 wherein the binding interactions are determined by:

calculating the free energy of binding between the protein structural variant model and the docked molecule; and

decomposing the total free energy of binding based on the interacting residues in the protein active site.

12. The method of claim 9 wherein:

after the protein structural variant models derived from a particular genetic polymorphism are generated, selected model structures are analyzed to determine common structural features that are conserved throughout the selected models; and

the conserved structural features are used as a basis for structure-based drug design studies.

13. The method of claim 12 wherein the selected model structures represent the structural variants resulting from the most commonly occurring genetic polymorphisms.

14. The method of claim 12 wherein the selected model structures represent the structural variants resulting from genetic polymorphisms found in a specific patient subpopulation.

15. The method of claim 12 wherein the selected model structures represent structural variants derived from patients the receive a specific treatment regimen.

16. The method of claim 12 wherein the selected model structures represent structural variants derived from patients that exhibit a particular clinical responses to a given drug.

17. The method of claim 12 wherein the selected model structures represent structural variants derived based on the duration of a particular drug treatment.

18. The method of claim 9 wherein the structural variant models are stored in a relational database, comprising:

3-D molecular coordinates for the structural variants;

a molecular graphics interface for 3-D molecular structure visualization; and

functionality for protein sequence and structural analysis; and

database searching tools.

19. The method of claim 18 wherein the database further comprises observed clinical data associated with the genetic polymorphisms.

20. A computer-based method of selecting drug therapies for patients based on genetic polymorphisms, comprising:

obtaining amino acid sequences of a target protein that is the product of a gene exhibiting genetic polymorphisms, wherein the sequences represent different genetic polymorphisms;

generating 3-D protein structural variant models from the sequences;

computationally docking drug molecules with the target protein models;

energetically refining the docked complexes;

determining the binding interactions between the drug or potential new drug candidate molecules and the models; and

selecting drug therapies based on the drug or drugs that have the most favorable binding interactions with the structural variant models.

21. The method of claim 20 wherein the binding interactions are determined by:

calculating the free energy of binding between the protein structural variant and the docked drug molecule; and

decomposing the total free energy of binding based on the interacting residues in the protein active site.

22. The method of claim 20 wherein the structural variant-drug complex models are stored in a relational database comprising:

3-D molecular coordinates for the structural variant-drug complex models;

a molecular graphics interface for 3-D molecular structure visualization;

functionality for protein sequence and structural analysis;

database searching tools; and

observed clinical data associated with the genetic polymorphisms.

23. A computer-based method for predicting clinical responses in patients based on genetic polymorphisms, comprising:

obtaining one or more amino acid sequences for a target protein that is the product of a gene exhibiting genetic polymorphisms;

generating 3-D protein structural variant models from the sequences;

building a relational database of protein structural variants derived based on genetic polymorphisms and observed clinical data associated with particular polymorphisms exhibited in the patients, wherein the database comprises:

3-D molecular coordinates for the structural variant-drug complex models;

a molecular graphics interface for 3-D molecular structure visualization;

functionality for protein sequence and structural analysis; database searching tools; and

observed clinical data associated with the genetic polymorphisms;

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obtaining a target protein structural variant based on the same gene associated with a polymorphism in a patient;

generating a 3-D protein model based on the subject's gene sequence;

screening/comparing the 3-D model derived from the subject to the structures contained in the database by:

identifying structures in the database that are similar to the model derived from the subject; and

predicting a clinical outcome for the patient based on the clinical data associated with the identified structures.

24. A computer-based method for designing therapeutic agents that are active against biological targets that have become drug resistant due to genetic mutations, comprising:

obtaining a first 3-D protein structural variant model of a target protein against which a given drug has biological activity;

generating a second 3-D protein structural variant model of the target in which genetic mutations have occurred and against which the same drug is no longer biologically active;

comparing the structures of the first and second model to identify structural differences; and

performing structure-based drug design calculations in order to identify new drugs or modifications to the existing drug to bring about biological activity against the second model.

25. A computer-based method for identifying compensatory mutations in a target protein, comprising:

obtaining the amino acid sequence of a target protein containing multiple amino acid mutations that is expressed in a patient, wherein the structure of a form of the target protein that responds to a particular drug, including the active site, has been structurally characterized;

generating a 3-D structural model of the mutated protein;

comparing the structure of the mutated protein with the form of the protein that responds to the drug to identify structural differences and/or similarities arising from the mutations;

comparing the biological activities of the drug against both the mutated protein and the form of the protein that responds to the drug to determine the effects of the mutations on drug response; and

identifying the mutations in the protein that affect biological activity based on the comparisons.

26. A method for creating a 3-D structural polymorphism relational database, comprising:

obtaining one or more amino acid sequences of a target protein that is the product of a gene exhibiting a genetic polymorphism, wherein sequences represent different genetic polymorphisms;

generating 3-D protein structural variant models from the sequences;

energetically refining the models;

evaluating the quality of the models;

optionally obtaining associated clinical properties or data; and

inputting the model and any associated properties and/or data into a relational database.

27. The method of claim 26, wherein after energetically refining the models, the models are further refined.

28. A database created by the method of claim 26.

29. The database of claim 28, comprising variant structures of a selected target.

30. The database of claim 28 that comprises structures of proteases or polymerases.

31. The database of claim 28, wherein the proteases are viral proteases or polymerases.

32. The database of claim 28, wherein the viral proteases are human immunodeficiency virus proteases.

33. The method of claim 1, wherein the target is an enzyme.

34. The method of claim 33, wherein the enzyme is a protease or polymerase.

35. The method of claim 34, wherein the polymerase is a reverse transcriptase.

36. The method of claim 33, wherein the target is enzyme expressed by an infectious agent.

37. The method of claim 36, wherein the agent is a human immunodeficiency virus (HIV).

38. A computer system, comprising a database containing data representative of the three dimensional structure of polymorphic variants of a drug target.

39. The system of claim 38, wherein the target is a cell surface receptor or an enzyme.

40. The system of claim 39, wherein the enzyme is a protease or a polymerase.

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